Elevated Neutrophil/Lymphocyte Ratio is Associated with Appropriate Shock After ICD Implantation

Neutrophil/Lymphocyte Ratio and ICD

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Özet

Amaç: Nötrofil/lenfosit (N/L) oranı koroner arter hastalığı, akut miyokard infarktüsü ve kalp yetersizliği gibi kardiyovasküler hastalıkların prognozu ile ilişkilidir. Ancak implante edilebilen intrakardiyak defibrilatör cihazı (ICD) olan kalp yetersizliği (KY) hastalarında prognostik önemi bilinmemektedir. Bu çalışmada artmış N/L oranı ile ICD olan kalp yetersizliği hastalarında uygun ICD şoklama gelişimi arasındaki ilişkiyi göstermeyi amaçlamaktadır. Gereç ve Yöntem: Toplam ICD implante edilmiş KY olan 58 hasta çalışmaya dahil edildi. ROC eğrisi analizine göre: optimal N/L oranının ICD şoklamasını tahmin etmedeki ayırıcı değeri >2.54 bulundu ve duyarlılığı %59.3, özgüllüğü %87.1 di. Hastalar ayırıcı N/L değerine göre, düşük (grup I) ve yüksek (grup II) olarak iki gruba ayrıldı. Bulgular: Hastaların ortalama yaşı 60±10 di. ICD şoklama 27 (%47) hastada gözlendi. Bu 27 hastanın 11 (%29) tanesi Grup I de ve 16 (%80) tanesi Grup II (p<0.001) de yer aldı. Hasta kabulündeki N/L oranı, sağ ventrikül dilatasyonu, hemoglobin ve hematokrit seviyeleri, sistolik PA basıncı ve orta-ciddi mitral yetersizlik tek değişkenli analizde prognostik olarak anlamlı bulundu. Çok değişkenli logistik regresyon analiz modelinde, sadece N/L oranı (p:0.031, OR:4.013, %95 CI:1.135-14.180) ICD implante edilmiş KY olan hastalarda uygun ICD şoklaması gelişimi ile ilişkiliydi. Tartışma: Yüksek N/L oranının, KY olan hastalarda koroner arter hastalığından bağımsız, uygun ICD şoklamasını için kuvvetli bir belirleyicisi olduğunu gösterdik.

Anahtar Kelimeler

Nötrofil/Lenfosit Oranı; Kalp Yetersizliği; İntrakardiyak Defibrilatör; Şok

Abstract

Aim: Neutrophil/lymphocyte (N/L) ratio is associated with prognosis in cardiovascular diseases such as coronary artery disease, acute myocardial infarction, and heart failure (HF). However, its prognostic significance in HF patients with implantable cardioverter defibrillator (ICD) is unknown. The aim of this study was to evaluate the association between N/L ratio and the development of appropriate ICD shock in HF patients with implante ICD. Material and Method: A total of 58 consecutive HF patients with implanted ICD were enrolled into the study. According to the receiver operator characteristics curve analysis: optimal cut-off value of N/L ratio to predict appropriate ICD shock was found as >2.54, with 59.3% sensitivity and 87.1% specificity. Patients were categorized into two as lower (group I) or higher (group II) N/L ratio according to cut-off value of >2.54. Results: Mean age of patients was 60±10 years. ICD shock was observed in 27 (47%) patients. Among these 27 patients 11 (29%) patient was in Group I and 16 (80%) were in Group II (p<0.001). N/L ratio on admission, right ventricular dilatation, hemoglobin and hematocrit levels, systolic PA pressure and moderate to severe mitral regurgitation were found to have prognostic significance in univariate analysis. In multivariate logistic regression model, only N/L ratio (p=0.031, OR: 4.013, %95 CI: 1.135-14.180) remained associated with the development of ICD shock in HF patients with implanted ICD. Discussion: We demonstrated that higher N/L ratio was strongly independent predictor of appropriate ICD shock, independent of coronary heart disease risk factors in HF patients.

Keywords

Neutrophil/Lymphocyte Ratio; Heart Failure; Intracardiac Defibrillator; Shock

Introduction

White blood cells (WBC) count and subtypes reflect inflammation and have a prognostic value in cardiovascular disease [1]. Elevated neutrophil levels have found to be associated with increased mortality and worse outcomes in cardiovascular diseases [2,3]. In contrast, lymphopenia has been shown to be related to with poor prognosis in patients with coronary artery disease (CAD) and heart failure (HF) [4]. Neutrophil/lymphocyte (N/L) ratio combines the predictive value of two WBC cell types and seems to be a strong indicator of systemic inflammation [5]. Previous studies reported that N/L ratio is associated with increased mortality in patients with cardiovascular disease such as acute coronary syndromes, HF, and peripheral arterial disease [2,3,6,7].

Patients suffer from HF with reduced ejection fraction (EF) have a risk of developing malignant ventricular arrhythmias such as ventricular tachicardia (VT) and ventricular fibrilation (VF). Implantable cardioverter defibrillators (ICDs) can prevent sudden cardiac death due to these arrhythmias. Several primary and secondary prevention trials showed that ICDs were most effective therapy in the prevention of sudden cardiac death in HF patients [8,9].

We aim to investigate association between appropriate ICD shocks and N/L ratio in our ICD recipient population.

Material and Method

A total of 74 consecutive HF patients with implanted ICD were evaluated. Patients with severe renal and hepatic failure, acute myocardial infarction within 6 months, hyperthyroidism and hypothyroidism, chronic obstructive pulmonary disease, malignancy, acute infectious disease, and chronic systemic inflammatory disease were excluded. Finaly, a total of 58 HF patients with implanted ICD were enrolled in the study. Patients were followed up 1 year for the development of appropriate ICD shock. The study was performed in accordance with the Declaration of Helsinki for Human Research, and was approved by the institutional review board.

Hypertension was defined as blood pressure ≥ 140/90 mmHg on more than two occasions during office measurements or receiving antihypertensive treatment. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or receiving antidiabetic treatment. The presence of CAD was defined as having abnormal stress test results with evidence of ischemia, or documented coronary stenosis >50% on a coronary angiogram, or having a clinical history of CAD. Rhythm were evaluated. All patients underwent routine laboratory investigation at admission, and hemogram parameters were obtained before ICD implantation. White blood cell subtypes was measured using a Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Inc., Fullerton, California).

Transthoracic echocardiograms were performed during index hospitalization within the first 24 hours in all of the patients. Echocardiographic examinations were performed via Vivid 7 system (GE Medical System) with 2.5-5 Mhz probes. Ejection fraction was calculated by Modified Simpson method and left atrium size were evaluated according to the most recent guidelines [11]. Then, patients were classified into two as those with right ventricular (RV) dilatation and without RV dilatation ac-

cording to guidelines [11]. Mitral, tricuspid and aortic regurgitations were quantified according to recent guideline, and categorized as moderate to severe versus non moderate to severe [11]. Systolic pulmonary artery pressure was calculated by peak velocity of tricuspid regurgitation and estimated right atrial pressure [12].

Statistical analysis

Parametric data were expressed as mean±standard deviation or median (min-max), and categorical data as percentages. SPSS 14.0 (SPSS, Inc., Chicago, Illinois) was used to perform statistical procedures. Independent parameters were compared via Independent sample's t test, and if there was no normal distribution, via Mann Whitney U test with median and min-max ranges. Categorical data were evaluated by chi square test as appropriate. Correlation was evaluated by Spearman's correlation test. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut off point of N/L ratio (at which sensitivity and specificity would be maximal) for the prediction of appropriate ICD shock. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with use of the Z test. MedCalc (v12.7.8) was used to perform ROC curve analysis. We used univariate analysis to quantify the association of variables with development of ICD shock. Variables found to be statistically significant in univariate analysis were used in a multivariate logistic regression model with enter method in order to determine the independent prognostic factors of the development of appropriate ICD shock. A p value <0.05 was accepted significant.

Results

Mean age of patients was 60±10 years. A total of 58 consecutive HF patients with implanted ICD were evaluated. ICD shock was observed in 27 (47%) patients during follow-up. N/L ratio was significantly higher in patients who developed appropriate ICD shock than patients who did not developed appropriate ICD shock (2.5±0.5 vs 2.1±0.6, p=0.007, Figure 1).

According to the receiver operator characteristics curve analysis: optimal cut-off value of N/L ratio to predict ICD shock was found as >2.54, with 59.3% sensitivity and 87.1% specificity

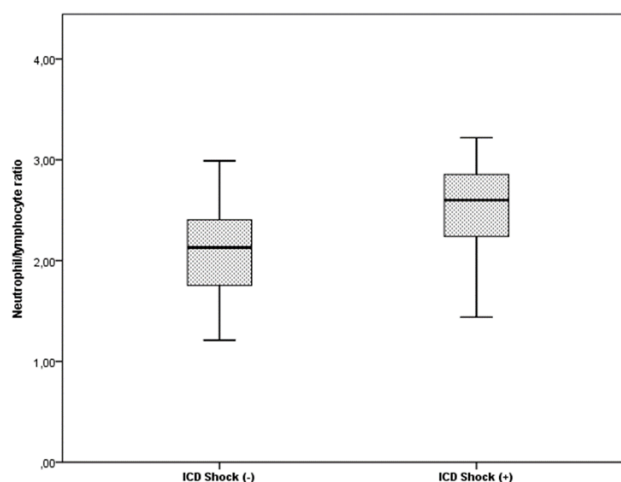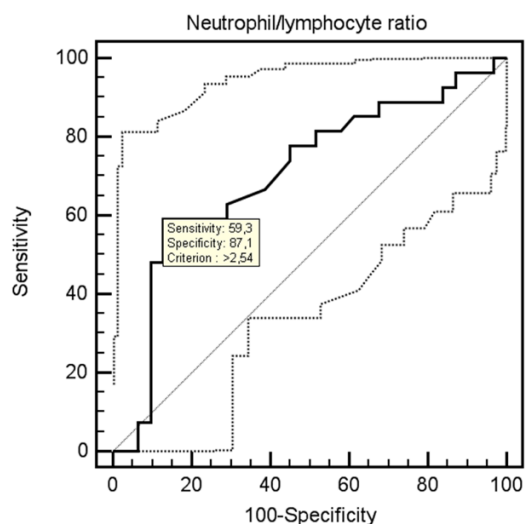Figure 1. Comparison of Neutrophil/lymphocyte ratio levels between two groups

Figure 2. ROC Curve of N/L ratio for development of appropriate ICD shock

Neutrophil/lymphocyte ratio

Sensitivity: 59,3
Specificity: 87,1
Criterion : >2,54

(Areas under the curve (AUC) 0.705, 95% CI 0.571 to 0.817, Figure 2). Patients were categorized into two as lower (group I) or higher (group II) N/L ratio according to this cut-off value. The clinical characteristics of patients with HF are summarized in Table 1. There was no significant association between N/L ratio and other clinical and laboratory findings (p >0.05).

Results of the univariate and multivariate logistic regression analyses for the development of ICD shock are listed in table 2. N/L ratio, RV dilatation, hemoglobin and hematocrit levels, systolic pulmonary artery pressure and moderate to severe mitral regurgitation were found to have prognostic significance in univariate analysis. In multivariate logistic regression model, only N/L ratio (p=0.031, OR: 4.013, %95 CI: 1.135-14.180) remained associated with appropriate ICD shock in HF patients with implanted ICD.

Discussion

This study, to the best of our knowledge for the first time in the literature, investigated the predictive value of N/L ratio for the development of appropriate shock after ICD implantation in patients with HF. We demonstrated that higher N/L ratio, poor right heart functions, severe mitral regurgitation, higher hemoglobin and hematocrit levels were associated with the development of ICD shock. However, even after controlling these parameters, we found that only higher N/L ratio was strongly independent predictor of appropriate ICD shock in HF patients. Heart failure is a common cause of mortality and morbidity. Approximately 60 % of patients with HF pass away due to dysrhytmias, frequently ventricular tachyarrhytmias [10]. ICD is the recommended therapy for the primary and the secondary prevention of ventricular arrhytmias. Several studies showed that some clinical and laboratory parameters such as low EF, high NYHA class, amiodarone treatment at implant, wide and fragmented QRS, microvolt T-wave alternans, heart rate variability, chronic obstructive pulmonary disease, history of renal failure, smoking, elevated BNP and heart-type fatty acid binding protein levels were associated with the development of arrhythmic events and ICD shock in HF patients [13-19]. In our study we observed that there is not a relationship between EF and ICD shock. Also, we found that high hemoglobin and hematocrit lev-

Table 1. Baseline characteristics of study patients

	All patients	Neutrophil/lymphocyte ratio		p
		≤ 2.54	> 2.54	
	(n:58)	(n:38)	(n:20)	
Mean age, years	60±10	62±10	58±11	0.178
Gender, male/female	51/7	33/5	18/2	1.000
Presence of Hypertension	32 (55%)	22 (58%)	10 (50%)	0.767
Presence of Diabetes mellitus	11 (19%)	7 (18%)	4 (20%)	1.000
Smoking	38 (66%)	24 (63%)	14 (70%)	0.818
Atrial fibrilation	6 (10%)	4 (11%)	2 (10%)	1.000
Ischemic heart disease	38 (66%)	24 (63%)	14 (70%)	0.818
Echocardiography at admission				
Left ventricular Ejection fraction, %	25 (10-45)	25 (10-43)	25 (20-45)	0.303
Systolic PA pressure, mmHg	20 (10-69)	20 (10-69)	25 (13-64)	0.241
Right ventricular dilatation	22(38%)	11 (29%)	11 (55%)	0.097
Moderate to severe Tricuspid regurgitation	20 (35%)	12 (32%)	8 (40%)	0.726
Moderate to severe Mitral regurgitation	20 (35%)	11 (29%)	9 (45%)	0.351
Moderate to severe Aortic regurgitation	2 (3%)	2 (5%)	0 (0%)	0.540
Laboratory findings				
Neutrophil/lymphocyte ratio	2.29±0.6	1.97±0.4	2.89±0.3	<0.001
Hemoglobin, gr/dL	13.9±1.5	13.9±1.5	13.8±1.6	0.783
Platelet counts, x103	229±78	237±68	215±94	0.330
Mean Platelet Volume, fL	8.9±1.2	8.8±1.1	9.2±1.4	0.262
Creatinine, mg/dL	1.2±0.4	1.17±0.4	1.26±0.4	0.464
Alanine aminotransferase, IU/L	27 (7-162)	25 (7-107)	33 (11-162)	0.609
Sodium. mmol/L	137±3	137±3	136±3	0.646
Potassium, mmol/L	4.4±0.6	4.4±0.5	4.3±0.3	0.597
Magnesium mg/dL	2.1±0.2	2.0±0.2	2.2±0.3	0.071
Medication at discharge				
Antiplatelet agents	54 (93%)	36 (95%)	18 (90%)	0.602
Beta-blockers	56 (97%)	38 (100%)	18(90%)	0.115
ACE inhibitors/ARB	51 (88%)	35 (92%)	16 (80%)	0.219
Statins	39 (67%)	26 (68%)	13 (65%)	1.000
Aldosteron antagonists	46 (79%)	31 (82%)	15 (75%)	0.734
Diuretics	37 (64%)	24 (63%)	13 (65%)	1.000
Amiodarone	29 (50%)	17 (45%)	12 (60%)	0.407
Digoxin	3 (10%)	4 (11%)	2 (10%)	1.000
Primary end point				
ICD Shock	27 (47%)	11 (29%)	16 (80%)	<0.001

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker

els, severe mitral regurgitation and poor right heart function are related to ICD shock in patients with HF. On the other hand, these variables do not predict ICD shock independently. We suppose that this association is due to increased left ventricular filling pressure.

White blood cell subtypes, especially the N/L ratio, has been showed as a prognostic marker and found to be related to worse clinical outcomes in cardiovascular disease [3,20-23].

Table 2. Univariate and multivariate logistic regression analyses of ICD shocking in patients with HF with implanted ICD

	Univariate			Multivariate		
Variable	p	OR	(95% CI)	p	OR	(95% CI)
Right ventricular dilatation	0.012	4.286	1.379-13.315	0.716	1.580	0.134-18.595
Hematocrit	0.017	1.191	1.032-1.375	0.597	1.219	0.585-2.539
Systolic PA pressure, mmHg	0.021	1.042	1.006-1.079	0.551	1.024	0.946-1.109
Neutrophil/ lymphocyte ratio	0.028	3.164	1.134-8.830	0.031	4.013	1.135-14.180
Hemoglobin (gr/dl)	0.029	1.539	1.045-2.268	0.930	1.098	0.134-9.002
Moderate to severe Mitral regurgitation	0.045	3.184	1.028-9.864	0.243	0.347	0.059-2.051

All the variables from Table 1 were examined and only those significant at a p < 0.05 level are shown in univariate analysis.
The multivariate logistic regression model with enter method included all univariate predictors.
CI: Confidence interval; OR: Odds ratio, Abbreviations in Table 1.

Neutrophils rank first among other leukocyte subtypes and has been the most valuable subtype as a prognostic marker for cardiovascular events [23]. Chia et al showed that the elevated neutrophil levels were associated with increased cardiac event. Furthermore, high neutrophil level was negatively correlated with EF and positively correlated with infarct size, after MI [24]. However, there is an inverse correlation between lymphocyte count and cardiovascular outcomes [4].

Recent studies have found that inflammatory pathways could play central role in HF. Previously as shown that there is association between incidence HF and biomarkers such as C-reaktive protein, interleukin-6, and tumor necrosis factor-α [25,26]. Leukocyte count increase during acute or chronic systemic inflammation [27]. The neutrophils influence the level and variation of leucocyte count most. Neutrophils mediate the inflammatory response to acute stress. Neutrophils and secreted cytokines by neutrophils seems to be effect several biochemical mechanisms and resulting in further tissue damage [28]. Lymphopenia is an indicator of physiologic stress and poor general health status [29]. Onsrud et al showed that during a stress, corticosteroid levels increase and lymphopenia is observed in stress due to increased lymphocytes apoptosis by elevated corticosteroid levels [30].

The reason for the association between increased N/L ratio and ICD shock is unclear. One possibility, increased proinflammatory mediators through increased neutrophils and decreased lymphocytes could increase developing worsening HF and contributes substrats which arrhythmias need. Moreover, preprocedural high neutrophil level is associated with subclinical inflamation, inversely preprocedural low lymphocyte level is related to high physiological stress and poor health status. As a result, high N/L ratio points out high risk patients more accurately.

Study Limitations

First, it is a retrospective study. Second, this single-center study had a small sample size, and included a mixture of patients receiving ICDs for primary or secondary prevention, and for biventricular pacing. Third, additional measurements of hemogram may provide useful information during follow-up.

In conclusion, if taken together, combination of 2 independent markers of inflammation, neutrophil-to-lymphocyte ratio, seems to be simple, sensitive, reproducible, inexpensive, and strong marker of reflecting systemic inflammation and has a prognostic and predicting value for worse cardiovascular outcomes.

Competing interests
The authors declare that they have no competing interests.

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